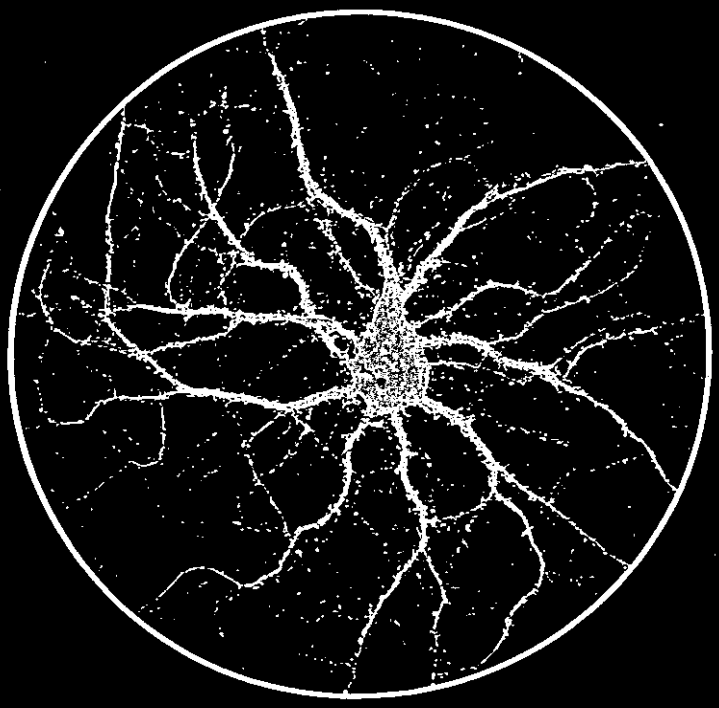
MOLECULAR BIOLOGY OF THE CELL

THIRD EDITION



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ıncts. If these minor cell proteins differ among cells to the same extent as the ıre abundant proteins, as is commonly assumed, only a small number of pro- differences (perhaps several hundred) suffice to create very large differences cell morphology and behavior.

Cell Can Change the Expression of Its Genes Response to External Signals [3]

ost of the specialized cells in a multicellular organism are capable of altering r patterns of gene expression in response to extracellular cues. If a liver cell exposed to a glucocorticoid hormone, for example, the production of several cific proteins is dramatically increased. Glucocorticoids are released during ods of starvation or intense exercise and signal the liver to increase the duction of glucose from amino acids and other small molecules; the set of teins whose production is induced includes enzymes such as tyrosine amino- sferase, which helps to convert tyrosine to glucose. When the hormone is no ger present, the production of these proteins drops to its normal level.

Other cell types respond to glucocorticoids in different ways. In fat cells, for mple, the production of tyrosine aminotransferase is reduced, while some r cell types do not respond to glucocorticoids at all. These examples illustrate neral feature of cell specialization—different cell types often respond in dif- nt ways to the same extracellular signal. Underlying this specialization are tures that do not change, which give each cell type its permanently distinc- character. These features reflect the persistent expression of different sets of s.

ne Expression Can Be Regulated at Many of the Steps the Pathway from DNA to RNA to Protein [4]

fferences between the various cell types of an organism depend on the par- r genes that the cells express, at what level is the control of gene expression ried? There are many steps in the pathway leading from DNA to protein, and h of them can in principle be regulated. Thus a cell can control the proteins it es by (1) controlling when and how often a given gene is transcribed (**tran- ptional control**), (2) controlling how the primary RNA transcript is spliced or erwise processed (**RNA processing control**), (3) selecting which completed NAs in the cell nucleus are exported to the cytoplasm (**RNA transport con- l**), (4) selecting which mRNAs in the cytoplasm are translated by ribosomes nslational control**), (5) selectively destabilizing certain mRNA molecules in e cytoplasm (**mRNA degradation control**), or (6) selectively activating, inacti- ng, or compartmentalizing specific protein molecules after they have been e (**protein activity control**) (Figure 9–2).

For most genes transcriptional controls are paramount. This makes sense se of all the possible control points illustrated in Figure 9–2, only transcrip- l control ensures that no superfluous intermediates are synthesized. In the

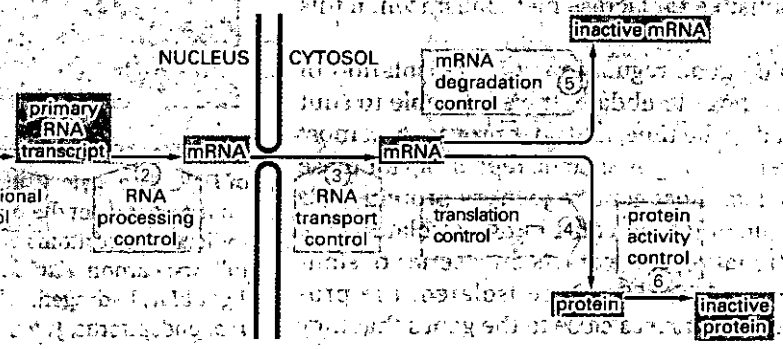

Figure 9–2 Six steps at which eucaryote gene expression can be controlled. Only controls that operate at steps 1 through 5 are discussed in this chapter. The regulation of protein activity (step 6) is discussed in Chapter 5; this includes reversible activation or inactivation by protein phosphorylation as well as irreversible inactivation by proteolytic degradation.

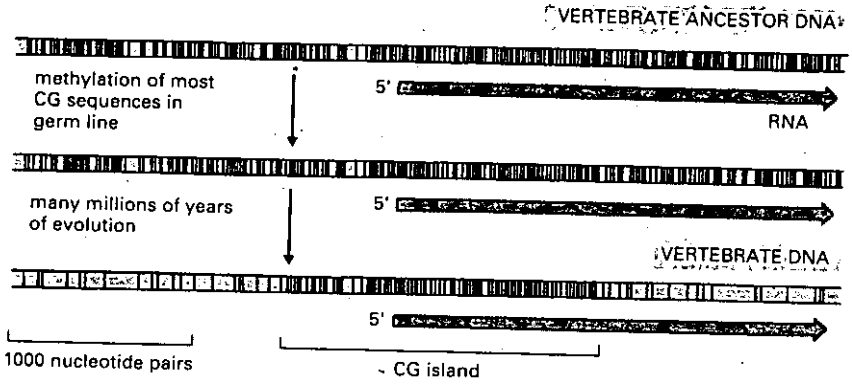

Figure 9–71 **A mechanism to explain both the marked deficiency of CG sequences and the presence of CG islands in vertebrate genomes.** A *black line* marks the location of an unmethylated CG dinucleotide in the DNA sequence, while a *red line* marks the location of a methylated CG dinucleotide.

Summary

The many types of cells in animals and plants are created largely through mechanisms that cause different genes to be transcribed in different cells. Since many specialized animal cells can maintain their unique character when grown in culture, the gene regulatory mechanisms involved in creating them must be stable once established and heritable when the cell divides, endowing the cell with a memory of its developmental history. Procaryotes and yeasts provide unusually accessible model systems in which to study gene regulatory mechanisms, some of which may be relevant to the creation of specialized cell types in higher eucaryotes. One such mechanism involves a competitive interaction between two (or more) gene regulatory proteins, each of which inhibits the synthesis of the other; this can create a flip-flop switch that switches a cell between two alternative patterns of gene expression. Direct or indirect positive feedback loops, which enable gene regulatory proteins to perpetuate their own synthesis, provide a general mechanism for cell memory.

In eucaryotes gene transcription is generally controlled by combinations of gene regulatory proteins. It is thought that each type of cell in a higher eucaryotic organism contains a specific combination of gene regulatory proteins that ensures the expression of only those genes appropriate to that type of cell. A given gene regulatory protein may be expressed in a variety of circumstances and typically is involved in the regulation of many genes.

In addition to diffusible gene regulatory proteins, inherited states of chromatin condensation are also utilized by eucaryotic cells to regulate gene expression. In vertebrates DNA methylation also plays a part, mainly as a device to reinforce decisions about gene expression that are made initially by other mechanisms.

Posttranscriptional Controls

Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made. Although these **posttranscriptional controls,** which operate after RNA polymerase has bound to the gene's promoter and begun RNA synthesis, are less common than *transcriptional control,* for many genes they are crucial. It seems that every step in gene expression that could be controlled in principle is likely to be regulated under some circumstances for some genes.

We consider the varieties of posttranscriptional regulation in temporal order, according to the sequence of events that might be experienced by an RNA molecule after its transcription has begun (Figure 9–72).

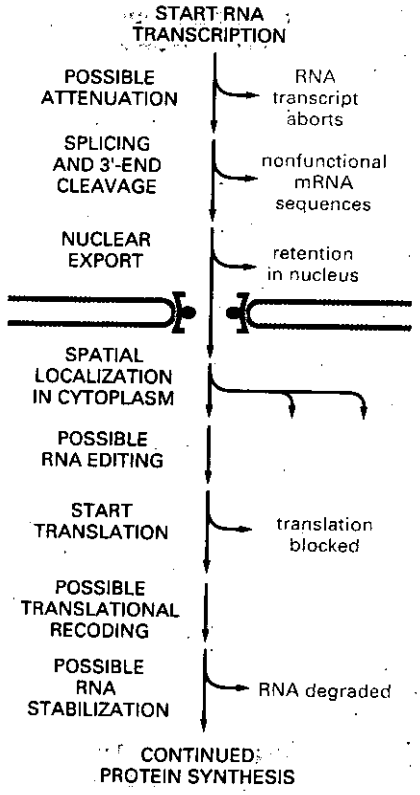

Figure 9–72 **Possible posttranscriptional controls on gene expression.** Only a few of these controls are likely to be used for any one gene.